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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SAMUEL H. GELLMAN, AHLKE HAYEN,
MARGERET A. SCHMITT, and FELIX N. NGASSA

Appeal 2010-000897
Application 10/648,089
Technology Center 1600

Before CAROL A. SPIEGEL, TONI R. SCHEINER, and
STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to an isolated, unnatural polypeptide compound. The Patent Examiner rejected

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

the claims as lacking both utility and enablement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The invention concerns "polypeptides comprising α-amino acids and cyclically-constrained β and/or γ-amino acids." (Spec. 1; 19-20). According to the Specification, "[t]hese novel, unnatural peptidomimetics are resistant or wholly immune to peptidase and protease degradation and are conformationally restrained." (*Id.* at 1: 20-22). The Specification describes the claimed compounds as being useful "as peptide mimetics that are not easily degraded by the action of proteolytic enzymes," e.g., "as probes to explore protein-protein interactions." (*Id.* at 19: 19-22).

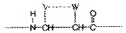
Claims 4 and 6 are on appeal. Claim 4 is representative and reads, in part, as follows:

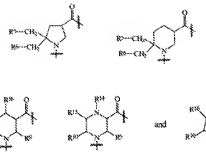
4. An isolated, unnatural polypeptide compound of formula:

wherein:

each X and each Z is independently variable and is selected from the group consisting of α-amino acid residues, β-amino acid residues, and γ-amino acid residues, provided that at least one X or Z is an α-amino acid residue and at least another two of X or Z are two cyclically-constrained β-amino acid residues; and

wherein each cyclically-constrained β-amino acid residue is independently selected from the group consisting of:





wherein V and W . . . .

(App. Br. 24.)

The Examiner rejected the claims as follows:

• claims 4 and 6 under 35 U.S.C. §101 "because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility." (Ans. 3); and

• claims 4 and 6 under 35 U.S.C. § 112, first paragraph as lacking enablement "since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility … , one skilled in the art clearly would not know how to use the claimed invention." (*Id.*).

UTILITY

The Issue

The Examiner's position is that the claimed compounds do not have a specific, substantial utility, because the disclosed use of the compounds for the "disruption of protein-protein interactions is a generic utility, and the questions that arise are 'which specific protein-protein interactions are contemplated and disclosed to be disrupted by Applicant?' and, 'to what end

are the interactions disrupted....'" (Ans. 5). According to the Examiner, the Specification is silent as to any specific protein-protein interaction that is disrupted and the effect of such disruption. (*Id.*). The Examiner found that Kim[2] examined the possibility that a synthesized β-proline decamer could substitute for the natural peptide, α-proline decamer, as a ligand of the protein prolifin. (*Id.* at 4). The Examiner also found that Kim concluded that that its β-proline decamer failed to bind to prolifin. (*Id.*). According to the Examiner, Kim addressed the possibility of studying protein-protein interactions and determined that its probe was unsuitable and therefore inoperative for use in such a study. (*Id.*). Additionally, the Examiner found that the Specification's disclosure of preparing libraries of the claimed compounds for use as research tools did not describe a substantial utility. (*Id.*).

Further, the Examiner found that the claimed compounds do not have a well-established utility because they lack a specific, substantial and credible utility that would be recognized by a person of ordinary skill in the art. (*Id.* at 6). The Examiner found that Schmitt,[3] while not contemporaneous with the instant application, provided evidence "that the art still does not provide a 'well established' utility" for compounds similar to those instantly claimed because Schmitt stated that its α/β-peptide foldamers "might mimic recognition surfaces on proteins and thereby disrupt

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[2] Yong Jip Kim, et al., "*Synthesis of (3R)-Carboxy Pyrrolidine (a β-Proline Analogue) and its Oligomer*," 10 BIOORGANIC & MEDICAL CHEMISTRY LETTERS, 2417-2419 (2000).

[3] Margaret A. Schmitt, et al., "*Residue Requirements for Helical Folding in Short α/β-Peptides: Crystallographic Characterization of the 11-Helix in an Optimized Sequence*," 127 J. AM. CHEM. SOC., 13130-13131 (2005).

specific protein-protein interactions…." (*Id.* at 5). According to the Examiner, Schmitt recognized potential utilities which were general and not specific. (*Id.*).

Appellants contend that "the claimed compounds have a specific, substantial, and credible utility as peptide mimetics that are not degraded by proteolytic enzymes" which is "explicitly disclosed in the specification…." (App. Br. 11, citing Spec. p. 19, l. 19 - p. 20, l. 25). Appellants assert that the Specification additionally disclosed that "[t]he utility of the compounds is directly linked to their structure." (*Id.* at 12). According to Appellants, "while the present compounds mimic natural proteins, they also adopt a far smaller set of conformations" due to the "cyclical constraints in the backbone." (*Id.*). Appellants assert that due to their structure, the compounds are useful in protein-protein binding experiments conducted under more rigorous conditions than would be available for more labile α-polypeptide compounds. (*Id.*).

Further, Appellants assert that there is a well-established utility for the claimed compounds, as evidenced by Seebach[4] and the Declaration of Dr. Gellman[5]. (*Id.* at 13, 19). According to Appellants, Seebach's synthesis and testing a γ-amino acid dipeptide to determine its ability to mimic a natural peptide and discovery that the dipeptide adopted a distinct and stable secondary structure "evidences a real-world, specific, substantial, practical,

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[4] Dieter Seebach, et al., "*Design and Synthesis of γ-Dipeptide Derivatives with Submicromolar Affinities for Human Somatostatin Receptors*," 42 AGNEW. CHEM. INT. ED. NO. 7, 776-78 (2003)

[5] Declaration of Samuel H. Gellman, dated Nov. 2, 2006.

credible and significant utility, in exactly the same fashion as the subject invention." (*Id.* at 14; Decl. ¶ 6).

The issue with respect to this rejection is whether the claimed compounds have a disclosed or well-established specific and substantial utility.

Findings of Fact

1. The Specification described the invention as being directed to unnatural "polypeptides comprising α-amino acids and cyclically-constrained β and/or γ-amino acids." (Spec. l; 19-20).

2. The Specification disclosed that the claimed compounds "find use as peptide mimetics that are not easily degraded by the action of proteolytic enzymes." (Spec. 19: 19-20).

3. The Specification disclosed that "the cyclically-constrained peptides of the present invention can be used as probes to explore protein-protein interactions." (*Id.* at 19: 20-22).

4. The Specification explained that "[b]ecause the compounds of the present invention are cyclically-constrained, they are more restricted conformationally than their strictly α-polypeptide counterparts." (*Id.* at 19; 22-24).

5. The Specification disclosed that "[l]ibraries of the subject compounds can also be prepared by automated means, thus providing access to a huge database which can be used as a tool to test, for example, potentially biologically-active agents." (*Id.* at 20; 1-3).

6. The Specification disclosed that a "highly useful aspect of the invention is that because the backbone is heterogenous, a portion of the

residues, such as the α-amino acids, provide functional diversity ... while the cyclically-constrained residues [i.e., β- or γ- amino acids] provide conformational specificity and stability." (*Id.* at 20: 4-8).

7. The Specification explains that the claimed compounds "are useful probes because the cyclically-constrained residues create secondary structures with high conformational stability at short oligomer lengths that are also resistant to enzymatic degradation. The invention thus enhances the control over γ-peptide folding preferences, thereby providing a larger 'toolbox' of probes to be used in investigating the function of naturally-occurring proteins." (*Id.* at 25; 6-11).

8. Seebach is a journal article that described the synthesizing γ-dipeptide derivatives and determining their use to mimic a peptide by testing the compounds for their affinities for cloned human somatostatin receptors. (Seebach, 776).

9. Seebach determined the binding affinities of the γ-dipeptides for the cloned human receptors by assessing displacement of a somatostatin dimmer from the receptor proteins. (*Id.* at 777).

10. Seebach stated that "[t]he results presented here are confirmative, surprising, and promising; they demonstrate that a 14-amino-acid cyclic disulfide hormone, somatostatin, can be mimicked by a [synthesized γ-dipeptide derivative]." (*Id.*).

11. Kim is a journal article describing the synthesis of a decamer of a β-amino acid analogue of L-proline which was found to possess a rigid secondary structure. (Kim, Abstract).

12. Kim described "simply replac[ing] the α-amino acid of a peptide with the corresponding β-amino acid and [examined] its conformation and

biological activity, and … chose a proline oligomer as [the] target peptide." (*Id.* at 2417).

13. Kim concluded that its synthesized β-proline decamer I "indicated a rigid secondary structure based on its CD spectrum; however, it failed to bind to prolifin, which show[ed] a tight hydrogen bonding to the amido backbone of the α-proline decamer II". (*Id.* at 2419).

14. Schmitt is a journal article that describes "the effects of variations in both α-residue and β-residue substitution on the favorability of helical folding among short α/β-peptides." (Schmitt, 13130).

15. Schmitt states, "Our findings will be useful for the generation of α/β-peptides that display specific side chain clusters. Foldamers of this type might mimic recognition surfaces on proteins and thereby disrupt specific protein-protein interactions or perform multifunctional catalysis of chemical reactions." (*Id.* at 13131).

16. Dr. Gellman's Declaration stated that utility disclosed in the Specification is "well-established and well-understood to a chemist of ordinary skill in the field of peptide mimetics." (Decl. ¶¶ 3, 5).

17. Dr. Gellman's Declaration explained that "the [claimed] compounds are useful as peptide mimetics that are not easily degraded by the action of proteolytic enzymes and that are capable of interrupting protein-protein interactions … because the claimed compounds adopt stable secondary conformation and contain tow or more unnatural β-amino acid residues and/or γ-amino acid residues in their backbones…." (Decl. ¶ 4).

18. Dr. Gellman's Declaration stated that while Seebach's compounds are slightly smaller than those presently claimed (dipeptides vs. tetrapeptides)

… [they] are otherwise closely related to the present compounds in that Seebach's compounds are constructed of γ-amino acids." (Decl. ¶ 6).

19. Dr. Gellman's Declaration stated that Seebach "clearly shows that compounds falling within the same class as those now claimed have a utility that is well-known to peptide chemists; namely to mimic natural peptides using unnatural polypeptide-containing compounds. The utility evidenced in [Seebach] is the same utility articulated in the present application." (*Id.*).

20. Dr. Gellman's Declaration provided examples using a Bcl-x_l/BH3 domain system to demonstrate that the utility asserted in the Specification is specific to the presently claimed compounds and that a chemist having ordinary skill in the art could easily confirm this utility without undue experimentation. (Decl. ¶¶ 9-19).

21. Dr. Gellman's Declaration stated that the "results of the experiments show that foldamer-based designs can provide tight-binding ligands for a large protein-recognition site … suggest[ing] that combining different foldamer scaffolds is also an effective (and perhaps general) strategy for protein ligand design." (Decl. ¶ 11).

22. Dr. Gellman's Declaration stated, "The results … reflect the exact utility that is stated within the patent application. The subject compounds mimic natural protein conformations in solution, but are significantly protected from proteolytic degradation by proteases and peptidases. The compounds are useful probes in the study of chemical and enzymatic interactions involving natural proteins." (Decl. ¶ 19).

Principles of Law

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

Brenner v. Manson, 383 U.S. 519, 534-35 (1966).

> Courts have used the labels "practical utility" and "real world" utility interchangeably in determining whether an invention offers a "substantial" utility. Indeed, the Court of Customs and Patent Appeals stated that "'[p]ractical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some *immediate benefit to the public.*" *Nelson* [*v. Bowler*], 626 F.2d [853,] 856 [(CCPA 1980)] (emphasis added). It thus is clear that an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the "substantial" utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public....
>
> Turning to the "specific" utility requirement, an application must disclose a use which is not so vague as to be meaningless. . . . Thus, in addition to providing a "substantial" utility, an asserted use must also show that that claimed invention can be used to provide a well-defined and particular benefit to the public.

In re Fisher, 421 F.3d 1365, 1371 (Fed. Cir. 2005).

"It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101." *Id.* at 1378.

Analysis

The record evidence contradicts the Examiner's finding that the Specification does not describe substantial utility for the claimed invention. The claimed compounds are directed to isolated, unnatural polypeptides comprising α-amino acids and cyclically-constrained β and/or γ-amino acids. (Claim 1, FF-1). The Specification and declaratory evidence disclosed, and the Examiner does not dispute, that these compounds find use as peptide mimetics that are not easily degraded by the action of proteolytic enzymes and can be used as probes to explore protein-protein interactions. (FF-2, 3, 17). That use meets the requirement for a substantial utility because it is practical, of real world value, and now made immediately available by Appellants to the public working in the peptide mimetic field. *See Fisher*, 421 F.3d at 1371.

The Specification and declaratory evidence also explained that the uses of the claimed compounds are directly linked to their structure. (FF-4, 6, 17). According to the Specification, the invention provides the field with peptides that are "more restricted conformationally than their strictly α-polypeptide counterparts" (FF-4), and "enhances the control over γ-peptide folding preferences, thereby providing a larger 'toolbox' of probes to be used in investigating the function of naturally-occurring proteins" (FF-7). These are well defined and particular benefits, uses which are not so vague as to be meaningless. *See Fisher*, 421 F.3d at 1371. Declarant Gellman explained that a person of ordinary skill in the field can design a probe according to the protein interaction of interest, and demonstrated this in the context of a Bcl interaction. (Decl. ¶ 10 et seq.) According to Declarant Gellman, Seebach and US Patent No. 6,958,384 evidence that probe design

was known in the peptide mimetic field, suited to the protein interaction of interest. (Decl. ¶¶ 6-7.) In view of this evidence, we find the Examiner's concern with the lack of working example compounds in the Specification to be misplaced. The requirement for a specific utility means that the utility must be well-defined and particular, not that specific example compounds must be provided.

The Examiner found that Kim addressed the possibility of studying protein-protein interactions and that Kim determined that its probe was unsuitable and therefore inoperative for use in such a study. (Ans. 4). According to the Examiner, Kim "shows that other compounds *hypothesized* to do what is instantly claimed *failed* to do so." (*Id.* at 11). We first note that Kim's compounds were different from the claimed compounds. More importantly, we are not persuaded that Kim concluded that its probe was a "failure" because it did not bind. Instead, Kim reported that the result confirmed information about the nature of binding by the α-peptide. This appears to be one of the benefits of using peptide mimetics.

Further, we agree with Appellants that the specific and substantial utility of constrained peptides was well-established in the peptide mimetic field. Seebach, for example, evidenced that using unnatural polypeptide compounds to mimic natural peptides was well-known to chemists in the art. (*See* FF-19). The fact that Seebach's compounds were smaller than those presently claimed (dipeptides vs. tetrapeptides), does not negate or otherwise render the reference inapplicable (*see* Ans. 4). This known utility is also not undermined by Schmitt's statement that its α/β-peptide foldamers "*might* mimic recognition surfaces on proteins and thereby disrupt specific protein-protein interactions…." (FF-15; Ans. 5 (emphasis added)). As the

Examiner acknowledged (Ans. 11) Schmitt hypothesized a utility for its constrained peptide compounds without testing those compounds for such utility, whereas Seebach tested a similar hypothesis and reported confirmative results that its peptide could mimic a naturally occurring peptide (FF-8, 10).

For these reasons, we find that Examiner has not established that the claimed invention lacks specific and substantial utility and we reverse the rejection. Because the enablement rejection relied only upon the utility rejection, we reverse it also. *See Fisher*, 421 F.3d at 1378.

CONCLUSION OF LAW

The claimed compounds have utility as peptide mimetic probes to explore protein-protein interactions. That use provides significant, presently available, well-defined, and particular benefits to the public.

SUMMARY

We reverse the rejection of claims 4 and 6 under 35 U.S.C §§ 101 and 112, first paragraph.

REVERSED

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